EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

22 June 2017
EMA/CHMP/644998/2016
Committee for Medicinal Products for Human Use (CHMP)

# Concept paper on an addendum on terms and concepts of pharmacogenomic features related to metabolism to the Guideline on the use of pharmacogenetic methodologies in the pharmacokinetic evaluation of medicinal products (EMA/CHMP/37646/2009)

| | |
|---|---|
| Agreed by Pharmacogenomics Working Party | April 2017 |
| Adopted by CHMP for release for consultation | 22 June 2017 |
| Start of public consultation | 10 July 2017 |
| End of consultation (deadline for comments) | 10 October 2017 |

Comments should be provided using this template. The completed comments form should be sent to PGWPSecretariat@ema.europa.eu


| | |
|---|---|
| Keywords | *Phenotype, genotype, methodologies, pharmacokinetics, metabolism* |



30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
**Telephone** +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
**Send a question via our website** www.ema.europa.eu/contact

# 1. Introduction

The vast majority of medicinal products are subject to enzymatic metabolism. This metabolism may result in detoxification, activation of the drug or to the formation of a toxic metabolite and therefore influences the effective and safe use of the product.

Amongst other enzymes, metabolism is dependent on multiple cytochrome P450 (CYP) isoenzymes. Since a number of these CYP enzymes are polymorphic in nature, e.g. CYP1A2, 2C9, 2C19, 2D6 and 3A4, the metabolism rate varies amongst individual patients, which may result in adverse drug reactions or lack of or increased efficacy.

In order to predict the efficacy and/or safety of medicinal products where genetic variants are of importance for the pharmacokinetics, optimal dose for an individual patient requires that the genetic polymorphism involved (genotype), and its likely effect on the drug metabolism, have been determined in an accurate and standardised manner. Facilitation of the use of a harmonised regulatory approach to the use of genotyping and its clinical implementation during assessment of new medicinal products, a harmonized nomenclature as well as optimal knowledge about the phenotype genotype relationship are essential.

# 2. Problem statement

At this moment, no consolidated definitions are available for different metabolic status and/or metabolic phenotypes. Terms such as poor/slow (lack of metabolic capacity), intermediate, extensive/normal (the most frequent category), rapid and ultrarapid/ultrafast (more rapid) metabolisers are used with some overlap and without clear definitions.

Guidance shall provide the relationship between different variants of genes encoding drug metabolism and the actual metabolic phenotype, enabling a consistent approach in this respect during the development of medicinal products.

# 3. Discussion (on the problem statement)

Although the importance of the metabolic phenotype for effective and safe use of medicinal products is acknowledged, at this moment there is an insufficient knowledge about the interpretation of genetic variants of the genes encoding drug metabolism to actual effects on the rate of drug metabolism.

Different pharmacogenomic service laboratories do not always analyse e.g. the genetic polymorphisms for predicting CYP1A2, 2C9, 2C19, 2D6 and 3A4 enzyme metabolic capacity in a harmonized and relevant manner.

Comparable and harmonised strategies with respect to the influence of genetic variation during drug development and subsequently in the SmPC of medicinal products in Europe should be aimed for. It is therefore considered important for regulatory evaluation to harmonize definitions and evaluation methods related to interindividual differences in drug metabolism of medicinal products.

The addendum will provide clear definitions of terms used for metabolic phenotyping, as well as to propose concepts regarding the translation of genotypes into the predicted metabolic phenotype, of significant importance for the correct treatment of patients.

The following aspects will be discussed in the proposed addendum:

1) Define concepts for different degree of genotype determined metabolism to be applied during development of medicinal products, i.e., Poor, Intermediate, Extensive, Ultrarapid metabolisers

2) Describe relationship, difference and pitfalls between geno- and phenotype determined metabolism and consequences for “measured” (from bioassay) vs “predicted” phenotype (from genotype) determination for appropriate recommendations to be made in the relevant parts of the SmPC, e.g. 4.1, 4.2, 4.5.. The prediction and value of predicted phenotypes shall be discussed.

It is suggested that the addendum does not consider genetic polymorphism of transporters, although this could also influence the drug’s pharmacokinetics.

## 4. Recommendation

The Committee for Human Medicinal Products’ (CHMP) Pharmacogenomics Working Party (PGWP) recommends drafting an *Addendum on terms and concepts of pharmacogenomic features related to metabolism* to the *Guideline on the use of pharmacogenetic methodologies in the pharmacokinetic evaluation of medicinal products* (EMA/CHMP/37646/2009).

## 5. Proposed timetable

It is anticipated that a draft Addendum will be available 4Q 2017 and will be released for 3 months of external consultation before finalisation.

## 6. Resource requirements for preparation

Development of the Addendum will be led by the PGWP.

A drafting group will be appointed with representation from the PGWP. Relevant experts from Committees or Working Parties as needed, e.g. Scientific Advice Working Party (SAWP) and Pharmacokinetic Working Party (PKWP) will be consulted.

Drafting work will be conducted primarily by email and teleconferences. Two Rapporteurs will take the lead. The PGWP will discuss draft versions at its regular meetings.

## 7. Impact assessment (anticipated)

By providing definitions and harmonizing evaluation methods related to metabolism of medicinal products, the addendum to the guideline will facilitate a harmonised use of knowledge with respect to the influence of genetic variation in the product information of medicinal products in Europe. Such harmonisation is expected to contribute to optimizing efficacy and preventing adverse drug reactions.

## 8. Interested parties

External consultation: pharmaceutical industry, academic centres of excellence in genomics; diagnostics industry and genomics service providers; patients’ organisations.

## 9. References to literature, guidelines, etc.


- Guideline on key aspects for the use of pharmacogenomics in the pharmacovigilance of medicinal products (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/11/WC500196800.pdf)

- Guideline on the use of pharmacogenetics methodologies in the pharmacokinetic evaluation of medicinal products (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/02/WC500121954.pdf)
- Reflection paper on methodological issues with pharmacogenomic biomarkers in relation to clinical development and patient selection (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/07/WC500108672.pdf)
- Reflection paper on co-development of pharmacogenomic biomarkers and assays in the context of drug development (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/07/WC500094445.pdf)
- Reflection paper on pharmacogenomic samples, testing and data handling (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003864.pdf)
- Draft Guideline on good pharmacogenomic practice (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/05/WC500205758.pdf)